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TRANSLATION OF PRIORITY DOCUMENT

FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT

BACKGROUND OF THE INVENTION

The present invention relates to a novel pharmaceutical composition having high bioavailability through improved dissolution, and a method for preparing it. The invention more particularly relates to a pharmaceutical composition for administration by oral route, containing an active ingredient of poor solubility.

Numerous active ingredients suffer from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and, consequently, poor bioavailability within the organism, following oral administration. The therapeutic dose required to be administered must thus be increased in order to obviate this disadvantage. This particularly applies to numerous hypolipemiant active ingredients, such as those belonging to the fibrate family.

Fenofibrate is a well-known hypolipemiant from the family of fibrates, which is commercially available in various doses (100 and 300 mg for example Secalip®) but in a form leading to poor bioavailability of the active ingredient. Indeed, due to it poor hydrosolubility, fenofibrate is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular and often varies from one person to another.

To improve the dissolution profile of fenofibrate and its bioavailability, thereby reducing the dose requiring to be administered, it would be useful to increase its dissolution so that it could attain a level close to 100%.

Moreover, for patient comfort, it is advantageous to seek a dosage form that only requires the medicament to be taken once daily while giving the same effect as one administered several times daily.

French patent 2,627,696 discloses a method for improving bioavailability of fenofibrate. This patent describes the effect of co-micronizing fenofibrate with a surfactant, for example sodium laurylsulfate in order to improve fenofibrate solubility and thereby increase its bioavailability. This patent teaches that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than the improvement that would be obtained either by adding a surfactant, or through solely micronizing the fenofibrate, or, yet again, through intimately mixing the fenofibrate and surfactant, micronized separately. The dissolution method employed is the conventional rotating blade technique (European Pharmacopoeia): product dissolution kinetics are measured in a fixed volume of the dissolution medium, agitated by means of a standardized device; a test was also carried out with an alternative technique to the European Pharmacopoeia, using the continuous-flow cell method.

The process of French patent 2,627,696 leads to a new dosage form in which the active ingredient, co-micronized with a solid surfactant, has improved fenofibrate dissolution, and thus increased bioavailability, which makes it possible, for a given level of effectiveness, to decrease the daily dose of the medicament: respective 67 mg and 200 mg instead of 100 mg and 300 mg.

However, the preparation method in that patent is not completely satisfactory inasmuch as it does not lead to complete bioavailability of the active ingredient, and suffers from several disadvantages. The technique of co-micronizing fenofibrate with a solid surfactant does, it is true, improve dissolution of the active ingredient, but this dissolution remains, however, incomplete.

There is thus a need to improve fenofibrate bioavailability in order to attain, over very short p riods of time, a level close to 100% (or, in any case, bett r than the following limits : 10% in 5 minutes. 20%

a medium consisting of 1200 ml water to which 2% Polysorbate 80 is added, with a blade rotation speed of 75 rpm), and this even when dissolution media having a low surfactant content are used.

The same need exists for other medicamental substances known to have poor dissolution and bioavailability. Examples of such substances are those of the fenofibrate family, such as for example gemfibrosil, cipofibrate, beclobrate, clinofibrate, simfibrate and bezafibrate, along with other substances such as glipizide, nifedipine, spironolactone, griseofulvine, acetazolamide, pipemidic acid, alprazolam, amphotericin B, atenolol, azathioprine, zidovudine, cortisone, econazole, furosemide, ketoconazole, loperamide, lovastatine, mesalazine, sucralfate, tolbutamide, papaverine, piroxicam, verapamil, etc., this list not being limiting.

Applicant has found that, surprisingly, it is possible to resolve this problem by a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrodispersible carrier. The present invention also relates to pharmaceutical compositions thus prepared.

The use is already known of a polymer, such as polyvinylpyrrolidone for producing tablets, in concentrations of the order of 0.5 to 5% by weight, at a maximum 10% by weight. In this case, the polyvinylpyrrolidone is used as a binder. Similarly, the use of a polymer such as hydroxymethylpropylmethyl cellulose as a granulation binder is known. Thus, European patent application 0,519,144 discloses pellets of a poorly soluble substance, omeprazole, obtained by spraying a dispersion or suspension of the active ingredient in a solution containing said polymer onto inert pellets in a fluidized-bed granulator. However, here again, the polymer (HPMC and HPC) is only used as a granulation binder, in an amount of about 50% by weight,

bearing in mind the presence of the inert pellets of a large size (about 700 μm) and the overall final weight leads to final active ingredient and polymer contents which are very low, of the order of barely a few percent based on the weight of the final covered pellet. Finally, it will be noted that the size of the inert pellets in this documents is fairly large, which, in the case of fenofibrate, would lead to a final formulation having a volume which is much too large for ready oral administration.

The use of polymer, such as polyvinylpyrrolidone for manufacturing "solid dispersions" is also known, obtained in general by co-precipitation, co-fusion or liquid-phase mixing followed by drying. What we have here is fixation of the active ingredient in isolated microparticles on the polyvinylpyrrolidone, which avoids problems of poor wetting of the solid and re-agglomeration of the particles. The article "Stable Solid Dispersion System Against Humidity" by Kuchiki et al., Yakuzaigaku, 44 No. 1, 31-37 (1984) describes such a technique for preparing solid dispersions using polyvinylpyrrolidone. The amounts of PVP here are very high, and the ratio between the active ingredient and PVP are comprised between 1/1 and 1/20. In the case however there is no inert carrier.

Nevertheless, nothing in the state of the art teaches nor suggest the present invention.

SUMMARY OF THE INVENTION

Thus, the present invention provides a composition comprising:

(a) an inert hydro-dispersible carrier covered with at least one layer containing a fenofibrate active ingredient in a micronized form having a size less than 10 μm, a hydrophilic polymer and, optionally, a surfactant; said hydrophilic polymer making up at least 10% by weight of (a); and

(b) optionally one or several outer phase(s) or layer(s).

In one embodiment, a surfactant is present with the active ingredient and the hydrophilic polymer.

The invention also provides a composition comprising a fenofibrate active ingredient having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80.

A method for preparing a pharmaceutical composition is also provided, comprising the steps of:

(a) preparing a fenofibrate suspension in micronized form with a particle size below 10 μm, in a solution of hydrophilic polymer and, optionally surfactant;

(b) applying the suspension from step (a) to an inert hydro-dispersible carrier;

(c) optionally, coating granules thus obtained with one or several phase(s) or layer(s).

Step (b) is preferably carried out in a fluidized-bed granulator.

The method can comprise a step in which products obtained from step (b) or (c) are compressed, with or without additional excipients.

The invention also provides a suspension of fenofibrate in micronized form having a size less than 10 μm, in a solution of hydrophilic polymer and, optionally, surfactant.

The invention will be described in more detail in the description which follows, with reference to the attached drawings.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a graph of a comparative study of the dissolution profile of a composition according to the invention, compared to that of Lipanthyl M®;

FIG. 2 is a graph illustrating a comparative study of the dissolution profile of a composition according to the invention and that of pharmaceutical products

FIG. 3 shows the dissolution profile of a composition according to the invention containing glipizide.

FIG. 4 shows the dissolution profile of the composition according to the invention containing nifedipine.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The term "active ingredient" is used in this document in its conventional sense and thus covers every substance having pharmacological, therapeutic, etc. activity. Compositions according to this invention are particularly suitable, in view of their improved dissolution profile, for administration of an active ingredient having poor solubility. This last term can be understood, in the framework of the invention, as an active ingredient having a solubility that is less than 1% by weight in pure water (or a solubility less than 10% in a dissolution medium constituted of water to which 2% Polysorbate 80 has been added). The solubility test is carried out using the rotating blade method as described in the European Pharmacopoeia. Mixtures of active ingredients are also suitable.

The person skilled in the art is able to determine, from the solubility test mentioned above, those active ingredients which can advantageously be employed in the framework of this invention.

The expression "in micronized form" in this invention means a substance in a particulate form, the dimensions of the particles being less than or equal to about 10 μm.

Advantageously, this dimension is less than or equal to 5 μm.

In the framework of this invention, the expression "inert hydrodispersible carrier" means any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, and which is soluble in an aqueous medium, notably in a gastric acid medium, or sufficiently

Examples of such excipients are derivatives of sugars, such as lactose, saccharose, or colloidal silica, or starch, hydrolyzed starch, (malto-dextrine), or cellulose, etc. Mixture are also suitable. The individual particle size of the inert hydrodispersible carrier can be, for example, between 50 and 500 micron.

The expression "hydrophilic polymer" in the invention should be taken to mean any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel. Examples of such polymers are polyvinylpyrrolidone, poly(vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, etc. Polymer blends are also suitable.

The preferred hydrophylic polymer is polyvinylpyrrolidone (PVP). The PVP used in this invention has, for example, a molecular weight comprised between 10,000 and 100,000, preferably for example between 20,000 and 55,000.

The term "surfactant" is used in its conventional sense in this invention. Any surfactant is suitable, whether it be amphoteric, non-ionic, cationic or anionic. Examples of such surfactants are: sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate or another ester of polyoxyethylene sorbitane, sodium dioctylsulfosuccinate (DOSS), lecithin, stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer®, etc. Mixtures of surfactants are also suitable.

The preferred surfactant is sodium laurylsulfate.

The compositions according to the invention can additionally contain any excipient conventionally us d in the pharmaceutical and chemical fields which is compatible with the active ingr dient, such as binders, fillers, pigments, disintegrating agents, lubricants,

able to be used in this invention we can cite: microcrystalline cellulose, lactose, starch, colloidal silica, talc, glycerol esters, sodium stearyl fumarate, titanium dioxide, magnesium stearate, stearic acid, cross-linked polyvinyl pyrrolidone (AC DI SOL®), carboxymethyl starch (Explotab®, Primojel®), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, etc.

Here, the expression "outer phase or layer" should be taken to mean any coating on the element (a) with the active ingredient (forming a "core"). Indeed, it can be useful to have available one or several phase(s) or layer(s) on top of the coated core. The invention thus covers a single core with one layer, but also several cores in a phase, as is the case of tablets which are formed from "cores" mixed with a phase.

This outer layer comprises conventional excipients. For example, an outer layer will comprise alkali reaction agents when the active ingredient is, for example, acido-labile.

An enteric coating can be provided, the enteric layer corresponding to an entero-soluble and gastro-resistant layer. For example, the enteric layer can be formed from methacrylic acid copolymer such as Eudragit®. The enteric layer can be deposited on an intermediate sub-layer.

It is also possible to provide a layer comprising additives, for the manufacture of tablets. In this embodiment, the outer layer comprises a disintegration agent and, for example, a lubricant; the thus covered and mixed granules can then be readily compressed and easily disintegrate in water.

The compositions according to the invention comprise, in general, based on the total composition weight excluding the outer phase or layer, an inert hydrodispersible carrier making up from 10 to 90% by weight, preferably 25 to 80% by weight, the active

preferably from 10 to 40% by weight, the hydrophilic polymer representing from 10 to 60% by weight, preferably 10 to 50% by weight, the surfactant making up from 0 to 10% by weight, preferably 0.1 to 3% by weight. The outer layer or phase if present, can make up to 80% by weight of the total weight, preferably up to 50% by weight.

The weight ratio of active ingredient to water-soluble polymer can for example be comprised between 1/10 and 4/1, preferably, for example, between 1/2 and 2/1.

When a surfactant is employed, the weight ratio surfactant/water-soluble polymer can be comprised for example between 1/500 and 1/10, preferably, for example, between 1/100 and 5/100.

In one embodiment, the composition according to the invention takes the form of tablets.

In another embodiment, the composition of the invention takes the form of granules enclosed inside a capsule, for example in gelatin.

The compositions of the invention are particularly suitable for administering active ingredients by oral route.

The composition according to the invention is prepared by a novel process comprising spraying a suspension of the active ingredient in a micronized form in a solution of a hydrophilic polymer and, optionally, a surfactant, onto the inert cores.

When a surfactant is present, the active ingredient can be co-micronized with the surfactant.

The method according to the invention consists in using the fluidized bed granulation principle, but with specific starting materials, in order to arrive at an improved dissolution profile and thus, at elevated bioavailability. In particular, the invention employs a suspension of the micronized active ingredient in a solution of a hydrophylic polymer and, optionally, a surfactant.

The fluidized-bed granulation technique is widely

capsules or tablets. Conventionally, according to the prior art, a powder or a mixture of powders (active ingredient + excipients) is put into suspension in the fluidized bed in a granulator, and a solution containing a binder and, optionally, a surfactant, is sprayed onto this bed to form granules. The fluidized-bed granulation technique is well known to those skilled in the art and reference should be made to standard works such as for example "Die Tablette", by Ritschel, Ed. Cantor Aulendorf, pages 211-212.

The invention, as has been indicated, comprises spraying a suspension of an active ingredient micronized with a water-soluble polymer onto an inert carrier. Following granulation, the granulate formed consists of crystals of, for example, lactose, which are isolated (or possibly agglomerated together by the PVP solution) and particles of active ingredient and PVP adhering to the crystal surface. The granulate could similarly be constituted of coated crystals which are agglomerated, or even of such an agglomerate having received a coating.

The compositions according to the invention can also be prepared by other methods, for example by spraying a solution of the micronized active ingredient onto the hydro-dispersible inert carrier.

The granulates thus obtained can, if desired, be provided with an outer coating or compressed into tablets, or form agglomerates.

The outer layer or layer is/are applied using conventional coating techniques such as coating in a pan or fluidized bed coater.

When the granulate obtained (whether subsequently coated or not) is compressed to form tablets, this step can be implemented using any conventional technique which is suitable, for example using an alternating or rotating compr ssing equipment.

The significant starting product is the suspension of the active ingredient. This suspension is prepared by

in a solution comprising the hydrophylic polymer and, optionally, a surfactant, in solution in a solvent. If a surfactant is employed, it is put into solution in the solvent (beaker + magnetic or vane stirrer). Next, the hydrophylic polymer (PVP) is dispersed, while stirring, in the solution previously obtained. Depending on polymer solubility, this either dissolves in the solution or forms a gel or a suspension having varying degrees of thickness. While still stirring, the micronized active ingredient is dispersed in the form of a fine shower into the above solution or suspension, to form a homogeneous suspension. The order of these steps can be reversed. The solvent employed can be aqueous or organic (for example ethanol). For example demineralized water can be used.

The active ingredient concentration in the suspension is from 1 to 40% by weight, preferably from 10 to 20%.

The hydrophylic polymer concentration in the suspension is from 1 to 40% by weight, preferably 5 to 20%.

The surfactant concentration in the suspension is from 0 to 10% by weight, preferably 1 to 5%.

The invention also covers this novel suspension.

Without wishing to be tied down to a specific theory, applicant believes that this novel method, through the use of a micronized active ingredient suspension in a hydrophilic polymer solution, enabled a novel composition to be obtained in which the active ingredient is in a non-re-agglomerated form.

The following examples illustrate the invention without limiting it.

Example 1 Preparation of a pharmaceutical composition of fenofibrate according to the invention

A composition containing, as the element a), micronized fenofibrate, Plasdone®, Capsulac® and sodium lauryl sulfate was prepared.

The micronized fenofibrate had a particle size of

The Plasdone K25® corresponds to a polyvinylpyrrolidone PVP ISP and the Capsulac 60® corresponds to a coarse crystal lactose monohydrate (particle size between 100 and 400 µm) (Meggle).

The sodium laurylsulfate (7g) is dissolved in water (demineralized water, 1750 g) and the micronized fenofibrate (350 g) is put into suspension in the mixture obtained (for example using a helix stirrer at 300 rpm for 10 minutes, then using an Ultra Turrax agitator at 10,000 rpm, for 10 minutes). Following this, the PVP (350 g) is added while still agitating, stirring (helix stirrer) being continued until the latter had dissolved (30 minutes). It is all passed through a sieve (350 µm) to eliminate possible agglomerates.

Separately, the lactose (400 g) is put into suspension in a fluidized air bed granulator (of the Glatt® GPCG1 - Top Spray type or equivalent) and heated to a temperature of 40°C.

The fenofibrate suspension is sprayed onto the lactose. This step is carried out under the following conditions: spraying pressure : 2.1 bar, air throughput 70 m^3/h, air inlet temperature: 45°C; air outlet temperature: 33°C; product temperature 34°C; duration of spraying: 3 h.

The granulate thus obtained can be put inside capsules or transformed into tablets. Any suitable conventional technique for preparing such dosage forms can be used.

For transformation to tablet form, one will mix 191 g of the granulate obtained (using for example a mixer-grinder type mixing apparatus, a planetary mixer or turn-over mixer), with the outer phase having the following composition:

- 56 g Polyplasdone XL® (cross-linked polyvinylpyrrolidone ISP, as described in the USA Pharmacopoeia "USP - NF" under the name of crospovidone,

- 3.5 g sodium stearyl fumarate (Mendell, U.S.A.); and

- 2 g Aerosil® 200 (colloidal silica).

The cross-linked polyvinylpyrrolidone, the microcrystalline cellulose, the sodium stearyl fumarate and the colloidal silica are respectively, disintegration agents, binders, lubricating and flow enhancing agents.

The tablet can be obtained on an alternating compression machine (for example Korsch EKO) or a rotary machine (for example Fette Perfecta 2).

One thus obtains tablets having the following composition, expressed in mg:

- element (a) :

micronized fenofibrate	100.0
PVP	100.0
Lactose	114.3
sodium laurylsulfate	2.0

- outer phase (or layer) :

cross-linked PVP	92.7
microcrystalline cellulose	145.7
sodium stearyl fumarate	5.8
colloidal silica	3.3

Example 2: Dissolution of a composition according to the invention and a composition according to the prior art.

a) dissolution medium and procedure for measuring dissolution.

A dissolution medium which is discriminating, in other words one in which two products having very different dissolution profiles in gastric juices will have very different dissolution curves is looked for; one thus attempts to eliminate uncertainties associated with a dissolution medium of the 0.1M sodium laurylsulfate aqueous type (a medium which has insufficient discrimination).

For this, an aqueous medium containing a surfactant, this being Polysorbate 80 (polyoxyethylene sorbitane mono-oleate) is used. This surfactant is readily

monograph in the Pharmacopoeias, and is thus easy to implement (being also a water-soluble liquid product). Other surfactants can also be used.

The rotating blade method (European Pharmacopoeia) is used under the following conditions: volume of medium: 1200 ml; medium temperature: 37°C; blade rotation speed: 75 rpm; samples taken: every 2.5 minutes. Determination of the amount dissolved is carried out by spectrophotometry. Test are repeated 6 times over.

b) Results

The composition according to the invention consisted of two tablets containing about 100 mg fenofibrate prepared according to example 1.

The prior art composition was Lipanthyl M® from Fournier, containing 200 mg fenofibrate (corresponding to micronized fenofibrate capsules containing 200 mg active ingredient along with sodium laurylsulfate, lactose, pregelatinized starch, cross-linked polyvinylpyrrolidone and magnesium stearate, in line with the teachings of French patent application 2,627,696).

The results obtained are shown graphically in FIG. 1, on which the percentage of dissolution is shown, the observed standard deviation being indicated between brackets.

These results clearly show that the compositions according to the invention have a dissolution profile which is distinctly better than that of the prior art compositions.

These results also clearly show that with the compositions of the invention, the standard deviation observed is distinctly lower than is the case with prior art compositions.

Example 3: Study of bioavailability of compositions according to the invention and prior art compositions.

A test of bioavailability on healthy volunteers was carried out.

The following compositions were tested.

- composition according to the invention: capsules containing granules prepared according to example 1, containing 200 mg fenofibrate.

- first composition according to the prior art: Lipanthyl® M from Fournier, containing 200 mg fenofibrate, identical to that in the previous example.

- second prior art composition: Secalip® in capsule form (300 mg fenofibrate in the form of three 100 mg capsules).

The study was carried out on 6 healthy volunteers receiving a single dose of fenofibrate, with a minimum 6-day rest period between administrations. The samples for pharmaco-kinetic analysis were collected after each administration at the following times: 0.5 h; 1 h; 2 h; 3 h; 4 h; 5 h; 6 h; 8 h; 10 h; 12 h; 24 h; 36 h; 48 h; 72 h; and 96 hours following administration of the medicament. Fenofibric acid content in plasma was measured for each sample.

The results obtained are given in table 1 below.

Table 1

Product	dose (mg)	Cmax (µg/mL)	tmax (h)	t1/2 (h)	AUC 0-t (µg.h/ml)	AUC 0-∞ (µg.h/ml)
Invention	200	5.4	6	23	148	162
Secalip® 100	3 x 100	1.1	25	39	53	56
Lipanthyl®	200	1.6	8.3	41	71	92

Cmax: maximum plasma concentration

tmax: time to reach Cmax

t1/2: plasma half-life

AUC 0 - t: area under the curve from 0 to t

AUC 0 - ∞: area under the curve from 0 to ∞.

The results clearly show that the compositions of the

improvement over compositions of the prior art, leading to a considerably enhanced bioavailability of the active ingredient compared to that obtained with compositions of the prior art.

Example 4: Comparison of the dissolution profile of compositions according to the invention and that of products currently on the German market.

On the German market, immediate or sustained-release fenofibrate formulations exist. Like in France, the 100 mg and 300 mg (conventional) forms coexist with 67 and 200 mg forms (having enhanced bioavailability, according to the teaching of French patent application 2,627,696). These products are as follows:

Fenofibrate - ratiopharm; Ratiopharm - Ulm;
Capsules;
Composition: 100 mg fenofibrate;
Excipients: lactose, corn starch, magnesium stearate, E 171 colorant, gelatine.

Durafenat; Durachemie - Wolfratshausen
Capsules;
Composition: 100 mg fenofibrate;
Excipients: lactose, corn starch, magnesium stearate, E 171 colorant, gelatine.

Normalip pro; Knoll - Ludwigshafen;
Capsules;
Composition: 200 mg Fenofibrate;
Excipients: Crospovidone, gelatine, monohydrate lactose, magnesium stearate, corn starch, sodium laurylsulfate, E 132 and E 171 colorants.

A comparison was made between:

- the tablet of the invention as prepared using example 1 (2 x 100 mg)
- **Normalip pro® (200 mg);**
- **Lipanthyl 200 M® (200 mg) (according to the prec ding exampl);**

- Durafenat® (2 x 100 mg)

The tests were implemented under the same conditions as in the previous examples. FIG. 2 summarizes the results.

These results clearly show that the compositions of the invention have a distinctly improved dissolution compared to prior art compositions.

Example 6: Preparation of compositions according to the invention containing other fibrate derivatives.

Compositions according to the invention in which fenofibrate was replaced by gemfibrosil, ciprofibrate or bezafibrate were prepared according to the method of example 1. The compositions were identical to that given in example 1, except for the active ingredient, which varied.

The dissolution profile of compositions thus obtained was compared to the one obtained for pharmaceutical preparations that were commercially available, as follows:

Gemfibrosil (450 mg), Lipur® tablets, - Parke Davis;
Ciprofibrate (500 mg), capsules, Lipanor® - Sanofi Winthrop;
BI-Lipanor® - 200 mg - Sanofi Winthrop;
Bezafibrate (200 mg), tablets, Bezifal® - Lipha Santé

The results of dissolution tests carried out according to example 2 clearly show that the dissolution profile of compositions according to the present invention is distinctly better than that obtained with the corresponding commercially-available dosage formulations.

Example 7: Study of dissolution profile of a composition according to the present invention containing other classes of active ingredient.

Other active ingredients, known for their poor solubility, were tested in this example, these being: glipizide and nifedipine.

The compositions according to the invention

(suspension of the active ingredient being carried out in 50.00 mg demineralized water):

Composition 1:

Glipizide	10.00 mg
Plasdone K29-32®	10.00 mg
Lactose EP D20®	80.00 mg

Composition 2:

Nifedipine (5μm)	10.00 mg
Plasdone K29-32®	15.00 mg
Lactose EP D20®	80.00 mg

The compositions according to the invention that were tested were prepared according to example 1, the various compounds being present in amounts calculated for 10 mg of glipizide or nifedipine active ingredient.

These compositions were compared to untreated active ingredients. The results of dissolution tests (carried out according to the method of example 2) are illustrated graphically in FIGS. 3 and 4 respectively, for glipizide or nifedipine active ingredients.

These results clearly show that the compositions according to the present invention have a dissolution profile which is improved compared to the untreated starting active ingredients.

Similar tests carried out on other poorly-soluble active ingredients, such as griseofulvine and spironolactone lead to similar results.

Obviously, the present invention is not limited to the embodiments described but may be subject to numerous variations readily accessible to those skilled in the art.

WHAT IS CLAIMED IS:

1.- A composition comprising:

(a) an inert hydro-dispersible carrier covered with at least one layer containing a fenofibrate active ingredient in a micronized form having a size less than 10 μm, a hydrophilic polymer and, optionally, a surfactant; said hydrophilic polymer making up at least 10% by weight of (a); and

(b) optionally one or several outer phase(s) or layer(s).

2.- The composition according to claim 1, in which a surfactant is present with the active ingredient and the hydrophilic polymer.

3.- The composition according to claim 1 or 2, in which the hydrophilic polymer is polyvinylpyrrolidone.

4.- The composition according to claim 2 or 3, in which the active ingredient and the surfactant are co-micronized.

5.- The composition according to any one of claims 2 to 4, in which said surfactant is sodium laurylsulfate.

6.- The composition according to any one of the preceding claims, in which, based on the weight of (a), said inert hydro-dispersible carrier makes up from 10 to 90% by weight, said active ingredient makes up from 5 to 50% by weight, said hydrophilic polymer makes up from 10 to 60% by weight, and said surfactant makes up from 0 to 10% by weight.

7.- The composition according to claim 6, in which, based on the weight of (a), said inert hydro-dispersible carrier makes up from 25 to 80% by weight, said active ingredient makes up from 10 to 40% by weight, said

hydrophilic polymer makes up from 10 to 50% by weight, and said surfactant makes up from 0.1 to 3% by weight.

8.- The composition according to any one of the preceding claims, in which the individual particle size of said inert hydro-dispersible carrier is comprised between 50 and 500 microns.

9.- A composition comprising a fenofibrate active ingredient having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80.

10.- A method for preparing a pharmaceutical composition according to any one of the preceding claims comprising the steps of:

(a) preparing a fenofibrate suspension in micronized form with a particle size below 10 μm, in a solution of hydrophilic polymer and, optionally surfactant;

(b) applying the suspension from step (a) to an inert hydro-dispersible carrier;

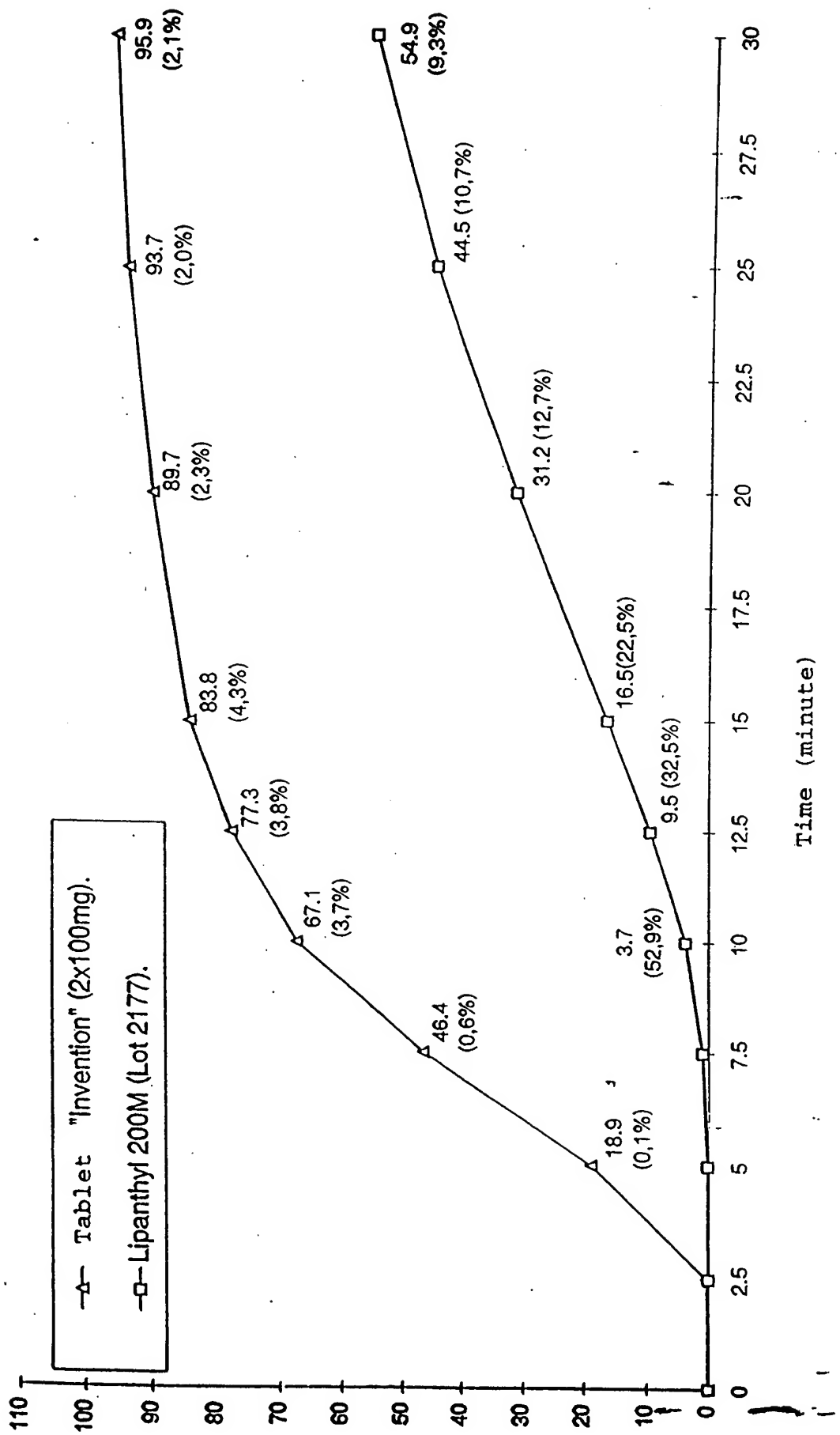
(c) optionally, coating granules thus obtained with one or several phase(s) or layer(s).

11.- The method according to claim 10, in which step (b) is carried out in a fluidized-bed granulator.

12.- The method according to claim 10 or 11, comprising a step in which products obtained from step (b) or (c) are compressed.

13.- A suspension of fenofibrate in micronized form having a size less than 10 μm, in a solution of hydrophilic polymer and, optionally, surfactant.

FIG 1


Tablet "Invention" (2x100mg).
Lipanthyl 200M (Lot 2177).
95.9 (2,1%)
93.7 (2,0%)
89.7 (2,3%)
83.8 (4,3%)
77.3 (3,8%)
67.1 (3,7%)
46.4 (0,6%)
18.9 (0,1%)
54.9 (9,3%)
44.5 (10,7%)
31.2 (12,7%)
16.5(22,5%)
9.5 (32,5%)
3.7 (52,9%)
110
100
90
80
70
60
50
40
30
20
10
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
25
27.5
30
Time (minute)

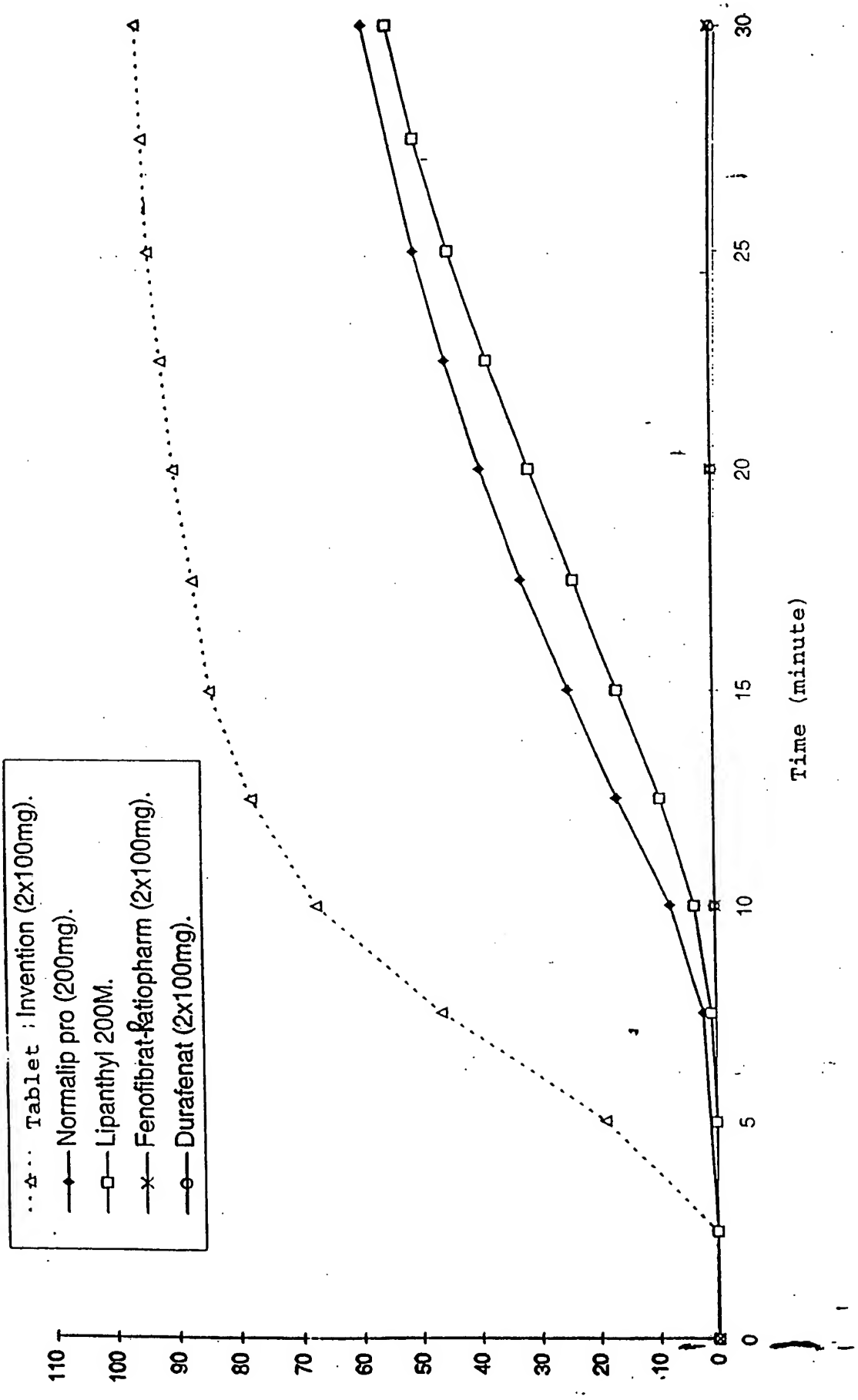

Tablet : Invention (2x100mg).
Normalip pro (200mg).
Lipanthyl 200M.
Fenofibrat-Ratiopharm (2x100mg).
Durafenat (2x100mg).
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (minute)

FIG 2

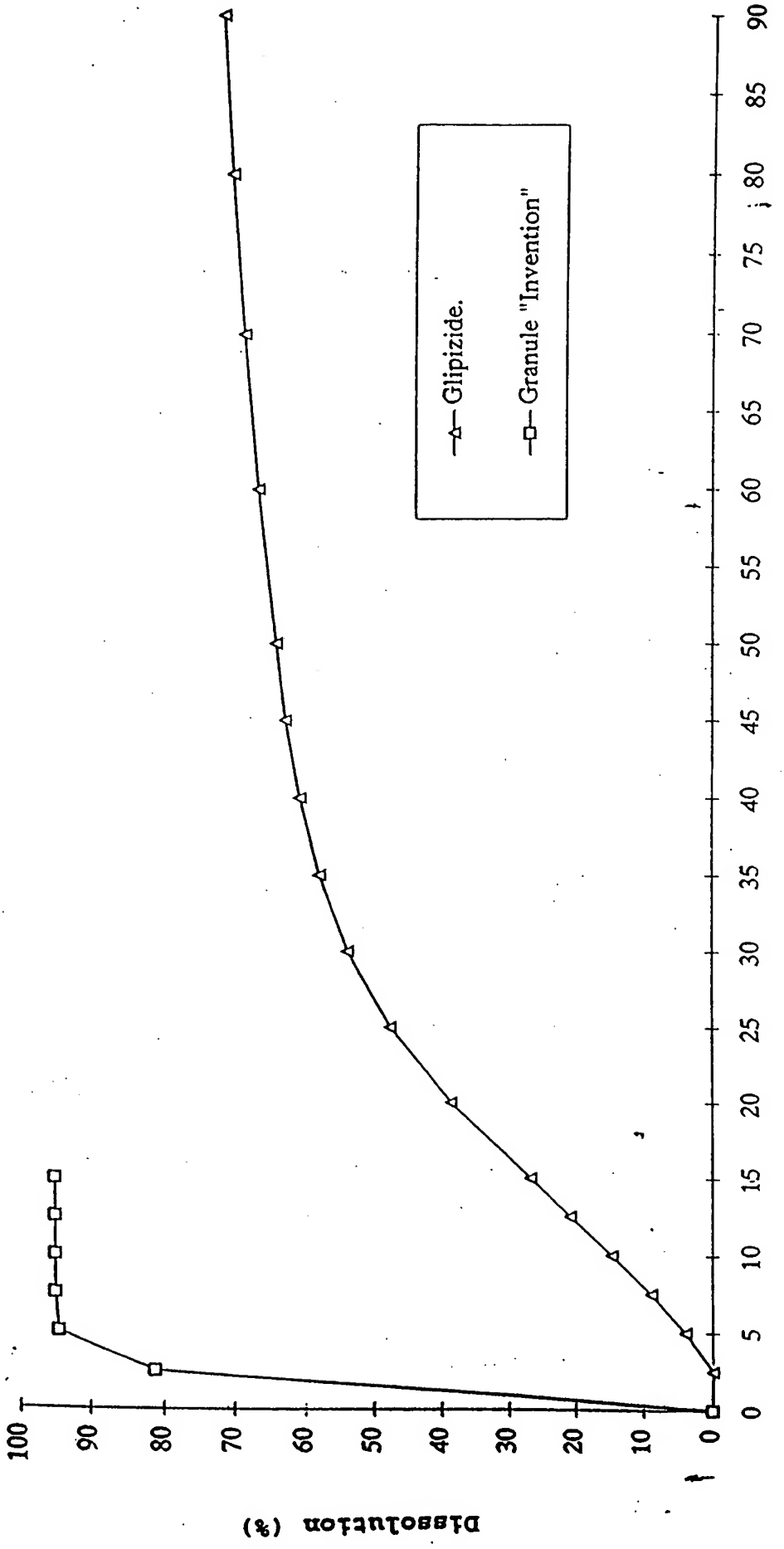

Dissolution (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
Time (minute)
Glipizide.
Granule "Invention"

FIG 3

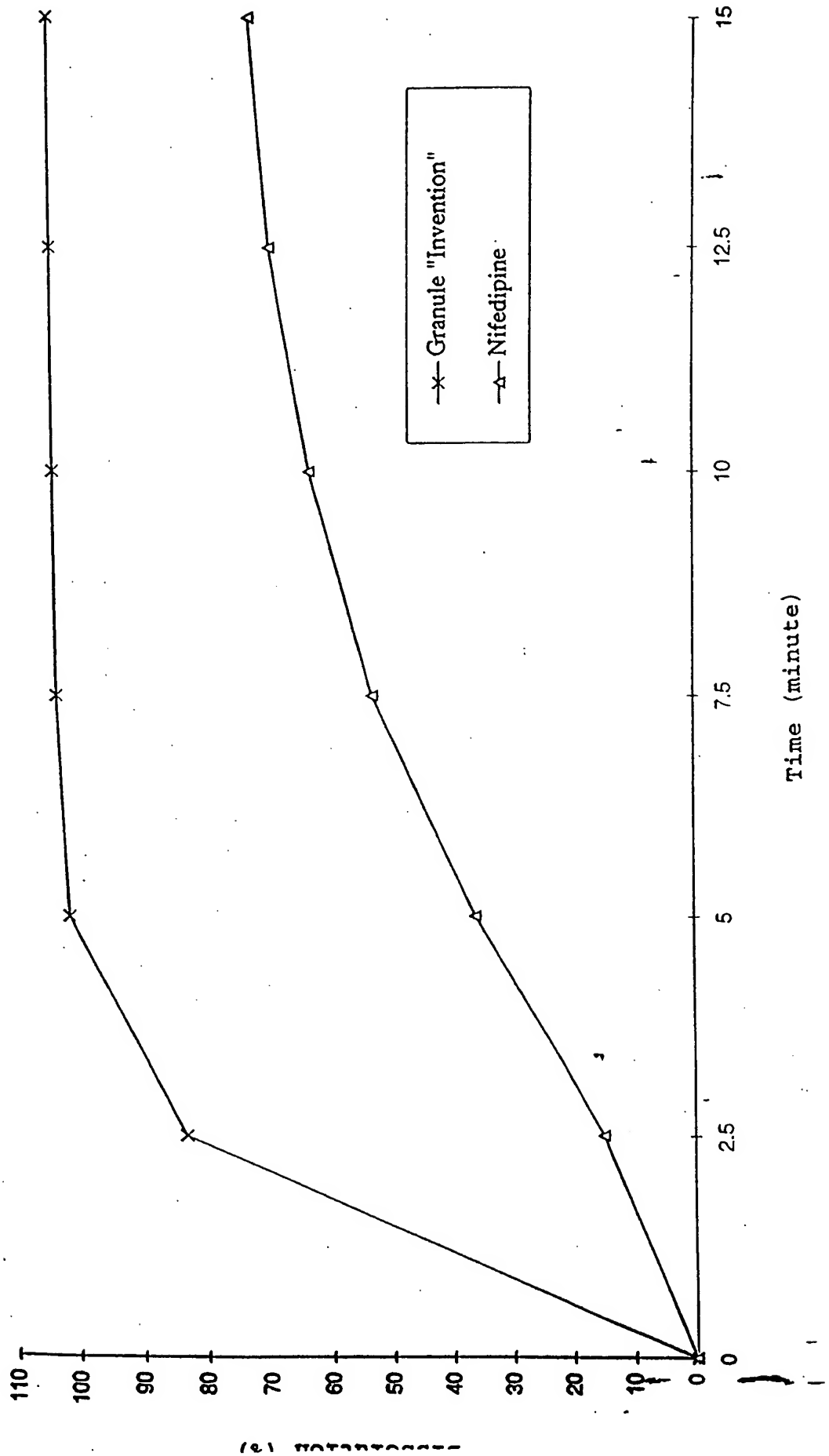

Granule "Invention"
Nifedipine
110
100
90
80
70
60
50
40
30
20
10
0
0
2.5
5
7.5
10
12.5
15
Time (minute)

FIG 4